博 士 学 位 論 文

予後不良が見込まれるギラン・バレー症候群のマーカー：多施設共同研究

近 畿 大 学 大 学 院
医学研究科医学系専攻
山　岸　裕　子

Doctoral Dissertation

Markers for Guillain-Barré syndrome with poor prognosis: a multi-center study

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Markers for Guillain-Barré syndrome with poor prognosis : a multi-center study

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Abstract

Guillain-Barré syndrome (GBS) is an acute monophasic neuropathy. Prognostic tools include the modified Erasmus GBS outcome score (mEGOS), Erasmus GBS respiratory insufficiency score (EGRIS), and the increase in serum IgG levels (ΔIgG) 2 weeks after intravenous immunoglobulin (IVIg) treatment. Given that proportions of GBS subtypes differ between Western countries and Japan, the usefulness of these tools in Japan or other countries remains unknown. We enrolled 177 Japanese patients with GBS from 15 university hospitals and retrospectively obtained mEGOS and EGRIS for all and ΔIgG status for 79 of them. High mEGOS scores on admission or on day 7 were significantly associated with poorer outcomes (unable to walk independently at 6 months). High EGRIS scores (≥5 points) were associated with an increased risk for mechanical ventilation. Patients with ΔIgG < 1,108 mg/dl had significantly poorer outcomes. We suggest that mEGOS, EGRIS, and ΔIgG in GBS are clinically relevant in Japan.

Key words : Guillain-Barré syndrome, prognostic marker, mEGOS, EGRIS

Introduction

Guillain-Barré syndrome (GBS) is an acute monophasic immune-mediated neuropathy, with considerably variable clinical severities and outcomes. Many patients with GBS recover within 6 months (*van Doorn, et al., 2008; Willison, et al., 2016*), In clinical trials in Western countries, which included only patients initially unable to walk independently, 15%–20% of patients were still unable to walk at 6 months from onset, and 3%–7% patients died (*van Doorn, et al., 2008; van Doorn, 2013; van den Berg, et al., 2014*). The mortality rate of patients with GBS is lower in Japan (～1%), and ～9% of patients are unable to walk independently at 6 months (*Saito, et al., 1999; Ogino, et al., 2000*). The current standard care for GBS includes plasmapheresis (PP) or intravenous immunoglobulin (IVIg) (*van der Meche, et al., 1992*). IVIg is more commonly used than PP in Japan. Early prediction of poor outcomes, such as inability to walk independently, might help determine whether, if any, such patients should be treated with more intensive immunotherapies and thereby improve outcomes in them.

Many factors associated with poor outcomes or the need for mechanical ventilation (MV) have been proposed (*McKhann, et al., 1988; Winer, et al., 1988; Durand, et al., 2006*). However, these data come only from Western countries.

The Erasmus GBS group developed and revised a prognostic model to combine some of the predictive factors described above and designated it as the modified Erasmus GBS outcome score (mEGOS) (*Walgaard, et al., 2011*). The same group also reported the Erasmus GBS respiratory insufficiency score (EGRIS), which predicted the need for MV within a week using patient's clinical characteristics on admission (*Walgaard, et al., 2010*). The same group also found a simple laboratory indicator for prognosis, the increase in serum IgG levels (ΔIgG) 2 weeks after the IVIg treatment; a larger ΔIgG was associated with a better outcome (*Kuitwaard, et al., 2009*). Because these prediction methods were based on data from patients in the Netherlands, the usefulness of these scores in other countries remains unknown.

In this report, we validated mEGOS, EGRIS, and ΔIgG in Japanese patients from 15 university hospitals and report on the retrospective efficacy of intensive immunotherapies in patients with poor prognosis predicted by mEGOS.

Materials and Methods

Patients

Our retrospective cohort comprised 177 patients with GBS whose clinical data were available at 6 months from admission. Between 2011 and 2015, these patients visited 1 of these 15 hospitals in Japan: the Kindai University Hospital, Teikyo University Hospital, Chiba University Hospital, Tokyo Medical and Dental University Hospital, Saitama Medical Center, Kyorin University Hospital, Tokushima University Hospital, Yamaguchi University Hospital, National Defense Medical College Hospital, Shinshu University Hospital, Fujita Health University School of Medicine Hospital, Kyushu University Hospital, Kagoshima University Hospital, Kanazawa Medical University

Hospital, and Nagoya University Hospital. All the 177 patients met the standard diagnostic criteria (Asbury and Cornblath, 1990). There were 105 (59%) men and 72 (41%) women (Table 1).

Table1. Clinical characteristics in 177 patients with GBS

		# of patients (%)	Mean (SD), range
Gender	**Men**	105 (59)	
	Women	72 (41)	
Age (year)	**≤ 40**	68 (38)	
	41 – 60	51 (29)	48.9 (19.7), 14 - 92
	≥ 61	58 (33)	
Preceding diarrhea		57 (32)	
Duration from onset to admission	**7**	52 (29)	
	4 – 7	74 (42)	7.3 (7.6), 0 - 80
	≤ 3	51 (29)	
GBS disability score(FG)			
On admission	**4 - 6**	85 (48)	3.1 (1.1), 0 - 5
	0 - 3	92 (52)	
At six months	**3 - 6**	19 (11)	1.1 (1.1), 0 - 6
	0 - 2	158 (89)	
mEGOS on admission	**< 7**	152 (86)	3.3 (2.4), 0 - 9
	7 - 9	25 (14)	
mEGOS on day 7 of admission	**< 10**	145 (82)	4.4 (3.8), 0 - 12
	10 - 12	32 (18)	
EGRIS	**< 5**	152 (86)	2.6 (1.6), 0 - 7
	5 - 7	25 (14)	
Patients on MV		30 (17)	
EGRIS in patients on MV			4.3 (1.5), 2 - 7
EGRIS in patient without MV			2.2 (1.4), 0 - 6

GBS, Guillain-Barré syndrome; FG, functional grade; mEGOS, modified Erasmus GBS outcome score; EGRIS, Erasmus GBS respiratory insufficiency score; MV, mechanical ventilation.

Clinical evaluations

We evaluated mEGOS and EGRIS for all the patients, and ΔIgG value for 79 patients. We assessed 175 patients with electrodiagnostic findings using the criteria of Ho and colleagues (*Ho, et al., 1995*). One hundred sixty-four patients were treated with IVIg or with IVIg plus combined immunotherapies (intensive immunotherapy). In this retrospective study, no specific treatment algorithm was followed; clinicians chose treatment modality according to their own judgment. We assessed outcomes on admission and at 6 months using the GBS disability score (functional grade: FG). Patients who were unable to walk independently (FG ≥ 3) at 6 months were classified as having poor outcomes, and patients who were able to walk independently (FG < 3) at 6 months were classified as having good outcomes.

Statistical analysis

Statistical analysis was performed using SPSS (version 20, IBM SPSS statistics) and the R statistical program version 2.13 (version 3.2.5, the R Foundation). $\chi 2$ test, Mann–Whitney U test, Pearson's product–moment correlation coefficient, and regression analysis were performed using SPSS. The R software was used to create receiver operating characteristic (ROC) curves and to set cut-off points. Categorical variables were analyzed

using $\chi 2$ tests or the exact probability method. Mann–Whitney U tests were performed for non-parametric data. P values < 0.05 were considered statistically significant.

Approval of ethics committees

This study was approved by the Institutional Review Boards of the participating universities.

Results

Results of treatment and outcomes

Of 176 patients with treatment, 99 (56%) patients were treated with a single cycle of IVIg, 32 (18%) with IVIg plus methylprednisolone pulse therapy (MP), 15 (9%) with IVIg plus PP, 12 (7%) with two cycles of IVIg, 6 (3%) with IVIg plus MP and PP, 4 (2%) with PP, 1 with MP plus PP, and 7 (4%) with no immunotherapy. In total, 65 (37%) were treated with intensive immunotherapy. On admission, 2 patients had FG = 0, 14 had FG = 1, 45 had FG = 2, 31 had FG = 3, 78 had FG = 4, and 7 had FG = 5. At 6 months, 66 patients had FG = 0, 70 had FG = 1, 22 had FG = 2, 6 had FG = 3, 10 had FG = 4, 2 had FG = 5 and 1 had FG=6.

Associations between mEGOS on admission and outcomes and between mEGOS on day 7 of admission and outcomes

Linear regression analyses revealed that higher mEGOS scores on admission significantly correlated with poorer outcomes ($p < 0.01$; Fig. 1A). The mEGOS on admission of 177 patients was 3.3 ± 2.4 (mean ± SD; range, 0–9). In total, 158 (89%) patients were able to walk independently at 6 months (FG ≤ 2) and 19 (11%) patients were unable to walk independently. The scores in 158 patients with good outcomes (3.0 ± 2.2, mean ± SD) were significantly lower than those in 19 patients with poor outcomes (5.5 ± 2.3; $p < 0.01$; Fig. 1B). Linear regression analyses revealed that higher mEGOS scores on day 7 of admission significantly correlated with poorer outcomes ($p < 0.01$; Fig. 1C). The mEGOS on day 7 of admission of 177 patients was 4.4 ± 3.8 (range, 0–12). The scores in 158 patients with good outcomes (3.8 ± 3.4) were significantly lower than those in 19 patients with poor outcomes (9.4 ± 2.6; $p < 0.01$; Fig. 1D).

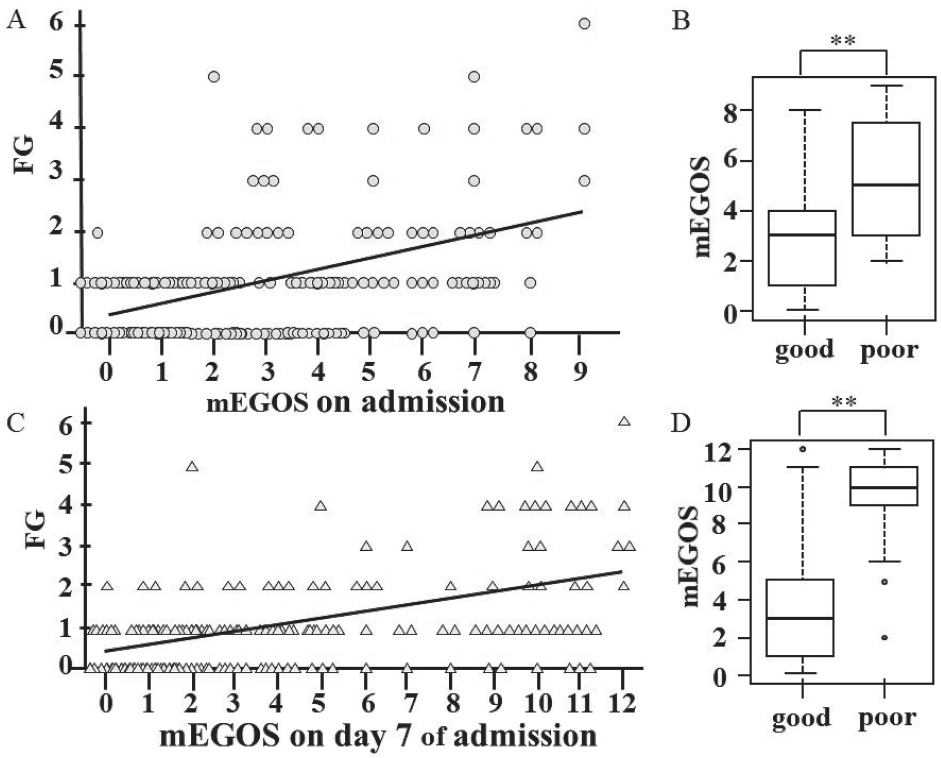

Figure 1. The modified Erasmus GBS Outcome Score (mEGOS) on admission and on day 7 of admission in 177 Japanese patients with GBS. (A) Linear regression analyses showed that higher mEGOS scores on admission were significantly associated with poorer outcomes as evaluated using functional grade at 6 months (FG, r = 0.436, $p < 0.01$). (B) Patients with good outcomes (FG < 3) had lower mEGOS scores than those with poor outcomes (**$p < 0.01$). (C) Higher mEGOS scores on day 7 of admission were significantly associated with poorer outcomes (r = 0.514, $p < 0.01$). (D) Patients with good outcomes had lower mEGOS scores than those with poor outcomes (**$p < 0.01$).

The cut-off point of mEGOS on admission

The R program suggested setting the cut-off of mEGOS on admission at 5 points (specificity = 76.5% and sensitivity = 57.9%). Scores of ≥5 points were associated with a higher proportion of patients with poor outcomes than scores of <5 points ($p < 0.01$; Fig. 2, left panel). Similarly, scores of ≥6 points were associated with a higher proportion of patients with poor outcomes ($p < 0.01$; Fig. 2, middle panel). If the cut-off point was set at 7 points, the specificity of the mEGOS to predict outcomes was much increased (specificity = 89.2% and sensitivity = 42.1%, $p < 0.01$; Fig. 2, right panel).

Need for MV and EGRIS

Patients with MV had higher scores on EGRIS than those without MV ($p < 0.01$; Fig. 3A). There were 30 (17%) patients who needed MV a week after admission. EGRIS was 2.6 ± 1.6 (0–7) in 177 patients; it was 4.3 ± 1.5 (2–7) in 30 patients with MV and 2.2 ± 1.4 (0–6) in 144 patients without MV (Table 1). Linear regression analyses showed that the scores were significantly associated with the outcomes as evaluated using FG ($p < 0.01$;

Fig. 3B). We set the cut-off at 5 points. Scores of >5 points were associated with poorer outcomes than scores of ≤5 points ($p < 0.01$; Fig. 3C).

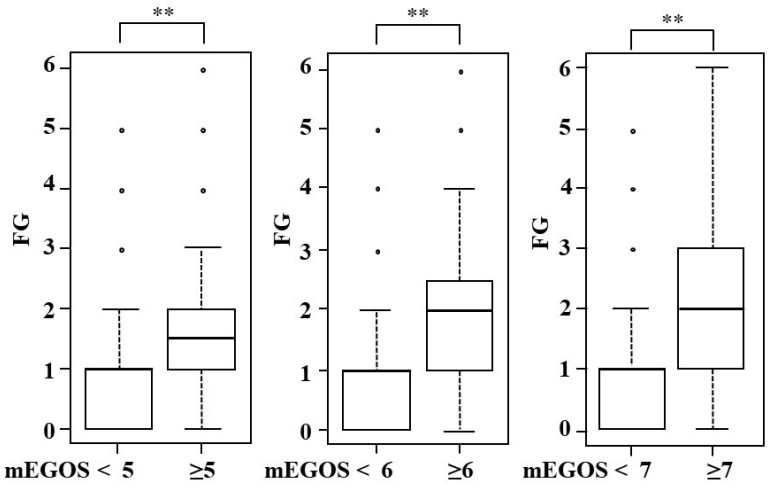

Figure 2. The cut-off point of mEGOS on admission in 177 Japanese patients with GBS. Significantly better outcomes were seen in patients with mEGOS < 5 points than in the rest of patients (left panel, $^{**}p < 0.01$), in patients with mEGOS < 6 points than in the rest (middle panel, $^{**}p < 0.01$), and in patients with mEGOS < 7 points than in the rest on the functional grade (FG) at 6 months (right panel, $^{**}p < 0.01$).

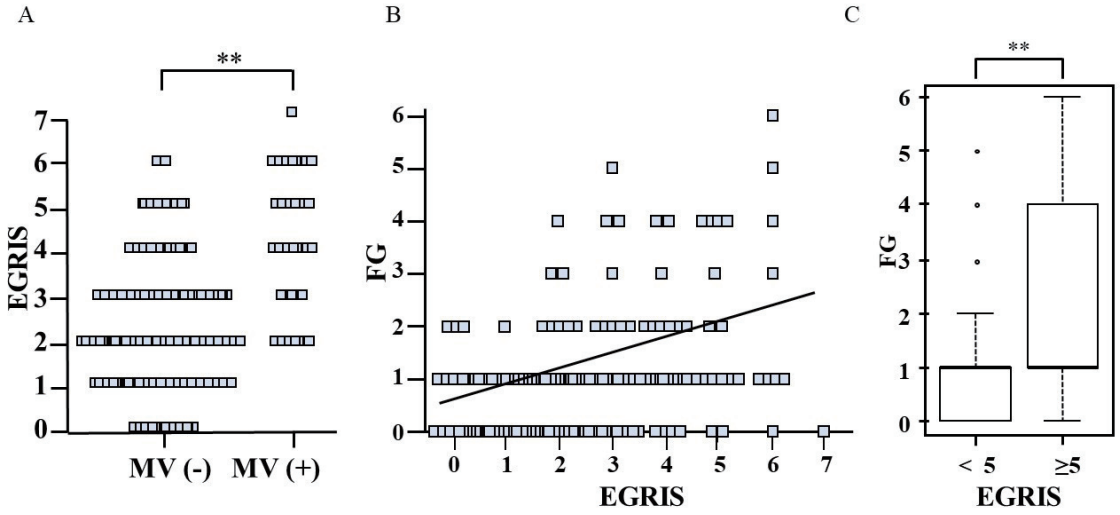

Figure 3. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) in 177 Japanese patients with GBS. (A) Patients without the need for mechanical ventilation (MV (-)) had lower scores on EGRIS than those who needed mechanical ventilation (MV (+), $^{**}p < 0.01$). (B) Higher EGRIS scores were also significantly associated with poorer outcomes as evaluated using functional grade at 6 months (FG) ($r = 0.387$, $p < 0.01$). (C) Patients with EGRIS < 5 points had better outcomes than those with EGRIS ≥ 5 points ($^{**}p < 0.01$).

Electrodiagnostic findings

Of 175 patients, 83 (48%) had acute immune demyelinating polyneuropathy (AIDP), 46 (26%) had acute motor axonal neuropathy (AMAN), and 46 (26%) had an unclassified type (*Ho, et al., 1995*). Of 19 patients with poor prognosis, 8 (42%) had AIDP, 9 (47%) had AMAN, and 2 (11%) had an unclassified type. Of 30 patients with MV, 22 (74%) had AIDP, 7 (23%) had AMAN, and 1 (3%) had an unclassified type. No significant difference in outcomes was observed between patients with AIDP and AMAN. Patients with AIDP needed MV significantly more frequently than those without AIDP (data not shown; $p < 0.01$). Patients with AMAN did not have a significant relationship with the need for MV ($p = 0.69$).

Increases in serum IgG and outcomes

Linear regression analyses showed no significant correlation between ΔIgG and outcomes (Fig. 4A). However, when the cut-off level was set at 1,108 mg/dl using the ROC curve (area under the ROC curve = 0.771, 95% CI: 0.644–0.899), patients with lower values of ΔIgG (<1,108 mg/dl) had significantly more severe clinical outcomes than those with higher values ($p < 0.01$; Fig. 4B). Furthermore, in 9 of 19 patients with poor outcomes, ΔIgG (528 ± 425 mg/dl; range, − 129 to 1,103 mg/dl) was significantly lower than that in 70 patients with good outcomes (1,004 ± 676 mg/dl, − 1,161 to 2,262 mg/dl; $p < 0.01$; Fig. 4C).

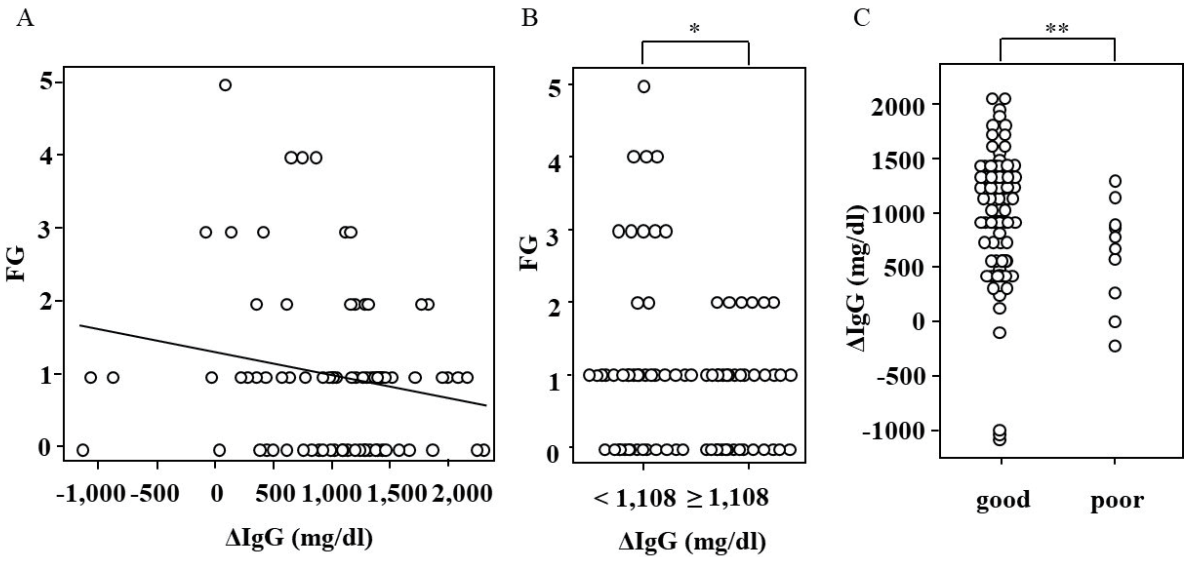

Figure 4. The increase in serum IgG levels (ΔIgG) 2 weeks after IVIg treatment in 79 Japanese patients with GBS. (A) Patients with higher ΔIgG tended to be able to walk independently at 6 months [functional grade (FG) < 3], but it did not reach statistical significance. (B) Patients with a high ΔIgG (>1,108 mg/dl) had significantly better outcomes than those with a low ΔIgG (*$p < 0.05$). (C) Patients with good outcomes had a higher ΔIgG than those with poor outcomes (**$p < 0.01$).

Immunotherapies

We analyzed whether FG at 6 months was influenced by a single cycle of IVIg or intensive immunotherapy. In 164 patients treated with IVIg or with intensive immunotherapy, no difference was observed in FG at 6 months between the treatment groups. We attempted to select patients on the basis of the prognosis predicted by mEGOS on admission. Although ROC analyses suggested setting the cut-off for determining the relationship between mEGOS and outcomes at 5 points, no difference in outcomes for patients with scores of ≥5 points was found between those treated with intensive immunotherapy and those treated with a single cycle of IVIg (Fig. 5, left panel). Similarly, no difference in outcomes for patients with scores of ≥6 points was found (Fig. 5, middle panel). Among the 25 patients with scores of ≥7 points, 16 patients treated with intensive immunotherapy had significantly better outcomes than 9 patients treated with a single cycle of IVIg ($p < 0.05$; Fig. 5, right panel). When the outcomes in patients treated with intensive immunotherapy were separately analyzed, IVIg plus MP was found to be associated with better outcomes than a single cycle of IVIg ($p < 0.05$). Patients treated with two cycles of IVIg tended to have better outcomes than those treated with a single cycle of IVIg, but the difference was not significant ($p = 0.06$). Similarly, patients treated with IVIg plus PP were found to have better outcomes, although the difference was not significant ($p = 0.08$).

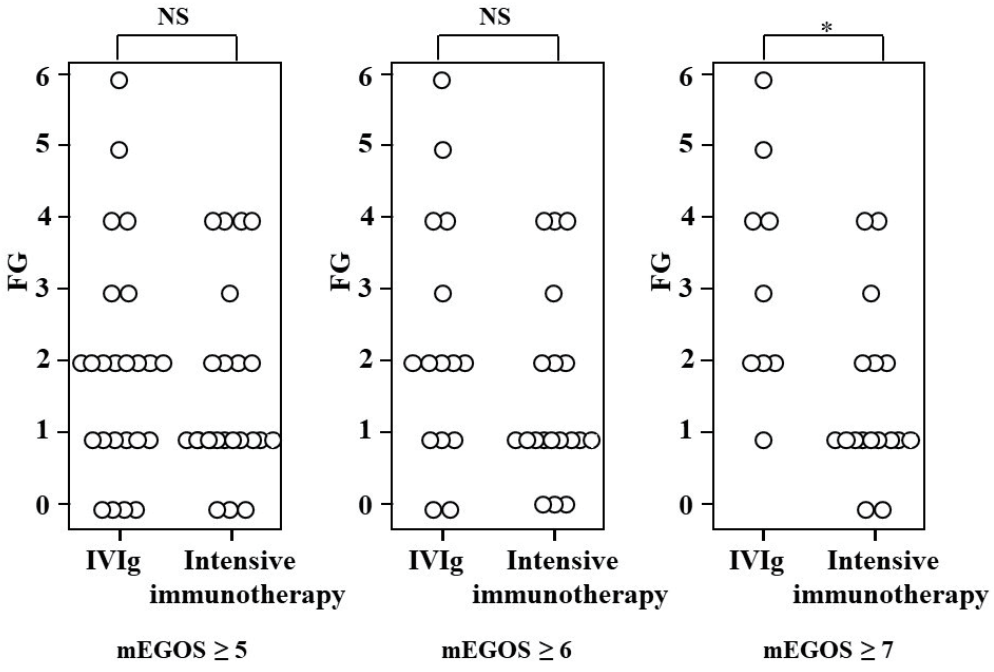

Figure 5. Immunotherapies in patients with GBS who had mEGOS ≥ 5, 6, or 7 points on admission. In patients with GBS who had mEGOS ≥ 5 or 6 points, no significant (NS) benefit of intensive immunotherapy on the functional grade (FG) at 6 months (left and middle panels) was seen. In patients with GBS who had mEGOS ≥ 7 points, 16 patients treated with intensive immunotherapy had significantly better outcomes than 9 patients treated with a single cycle of IVIg (*$p < 0.05$).

Discussion

The results of linear regression analyses in Japanese patients suggest that higher mEGOS scores on admission and on day 7 of admission significantly correlated with poor outcomes. This was consistent with the results of a previous study conducted in the Netherlands (*Walgaard, et al., 2011*). The study results indicate that mEGOS may be useful for predicting outcomes in Japanese patients with GBS.

Our results also suggest that EGRIS was a useful tool of GBS in Japanese patients. Because a previous study demonstrated that patients with a score of ≥5 points are at a high risk for the need for MV (*Walgaard, et al., 2010*), we set the cut-off at 5 points in our cohort. Patients with scores of ≥5 points needed MV significantly more frequently. Our data also suggests that a GBS subtype, AIDP, was associated with the need for MV, which is consistent with results from studies in Western countries (*Durand, et al., 2006*). EGRIS was also useful as a predictor of poor prognosis. As EGRIS points increased, more patients were unable to walk independently at 6 months. This is probably because EGRIS shared medical research council (MRC) sum scores with mEGOS that predicted prognosis.

We determined that the cut-off level for ΔIgG to predict outcome was 1,108 mg/dl. Patients with ΔIgG < 1,108 mg/dl walked independently at 6 months significantly less frequently than those with ΔIgG ≥ 1,108 mg/dl. In contrast, a previous study of ΔIgG divided patients with GBS into four groups with levels of <399, 399–730, 731–1,092, and >1,092 mg/dl, where the first and second groups had worse outcomes than the others, suggesting that the cut-off level was about 731 mg/dl. It remains unclear why the cut-off level was higher in Japanese patients. It might be associated with entry bias because our study enrolled patients regardless of the severity of their condition, in contrast to a previous study that included patients with FG ≥ 3 only (*Kuitwaard, et al., 2009*). A previous study suggested that a higher IgG metabolism was associated with a stronger immunoreactivity, and thereby poorer outcomes (*Kuitwaard, et al., 2009*). A presumed lower IgG metabolism in Japanese people is consistent with the reportedly lower mortality rate of patients with GBS in Japan (~1%) than that in Western countries (~5%) (*Saito, et al., 1999*). However, because the number of patients in this study was small and the pharmacokinetics of IVIg show considerable intra- and inter-patient variability, the differences in ΔIgG between the Netherlands and Japan may be attributed to such variations (*Koleba and Ensom, 2006; Roopenian and Akilesh, 2007; van Doorn, et al., 2011; Kuitwaard, et al., 2013*).

Our preliminary results from 25 patients predicted to have poor prognosis based on mEGOS on admission (≥7 points) showed that patients treated with intensive immunotherapy had significantly better outcomes than those treated with a single cycle of IVIg. In contrast, in all patients with GBS, including those with good prognosis, there was no difference in outcomes between those treated with and without intensive immunotherapy. These results suggest that we should select patients with poor prognosis for intensive immunotherapy. In addition, development of new therapeutic options, such as complement inhibition, may be needed for patients with poor prognosis. This issue is now under investigation (*Yamaguchi, et al., 2016; Davidson, et al., 2017*).

This study had several limitations, such as being a retrospective analysis of a relatively small number of

patients. In addition, because we chose patients based on the availability of clinical data from onset until 6 months after enrollment, severely affected patients unable to visit hospitals were excluded. Very mild cases might also have been excluded because there was no need for them to visit the hospital. The International GBS Outcome Study (IGOS) is a prospective, observational, multicenter cohort study that aims to identify the clinical and biological determinants and predictors of disease onset, subtype, course and outcome of GBS (*Jacobs, et al., 2017*). The results of our retrospective study need to be corroborated by those of such a prospective large-scale study as the IGOS.

In conclusion, mEGOS, EGRIS, and ΔIgG were found to be useful in Japan, as in the Netherlands. We determined the appropriate cut-off points of these tools for Japanese patients. Future prospective studies to examine the efficacy of intensive immunotherapy for patients with GBS with poor prognosis are warranted.

Acknowledgments

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